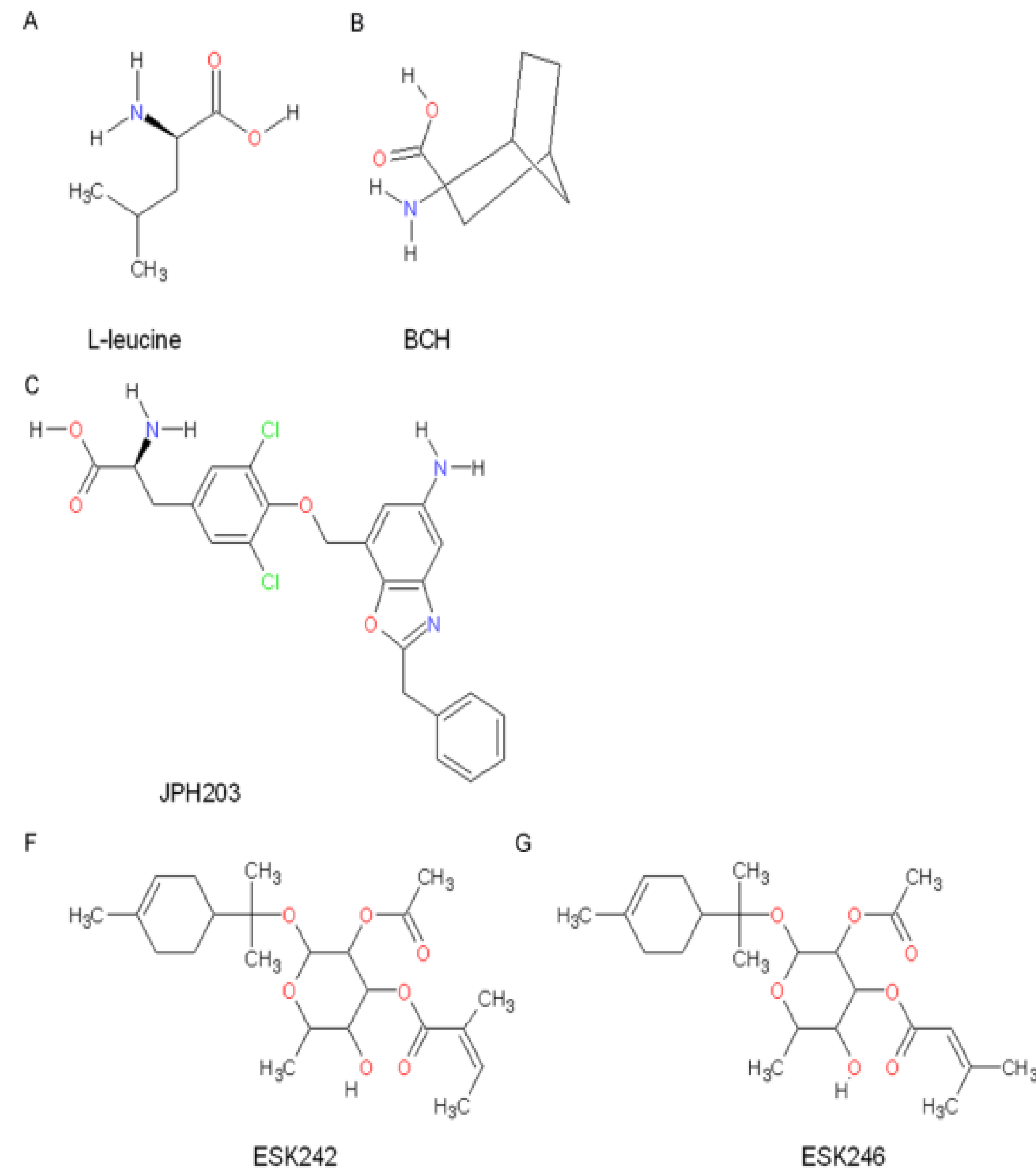
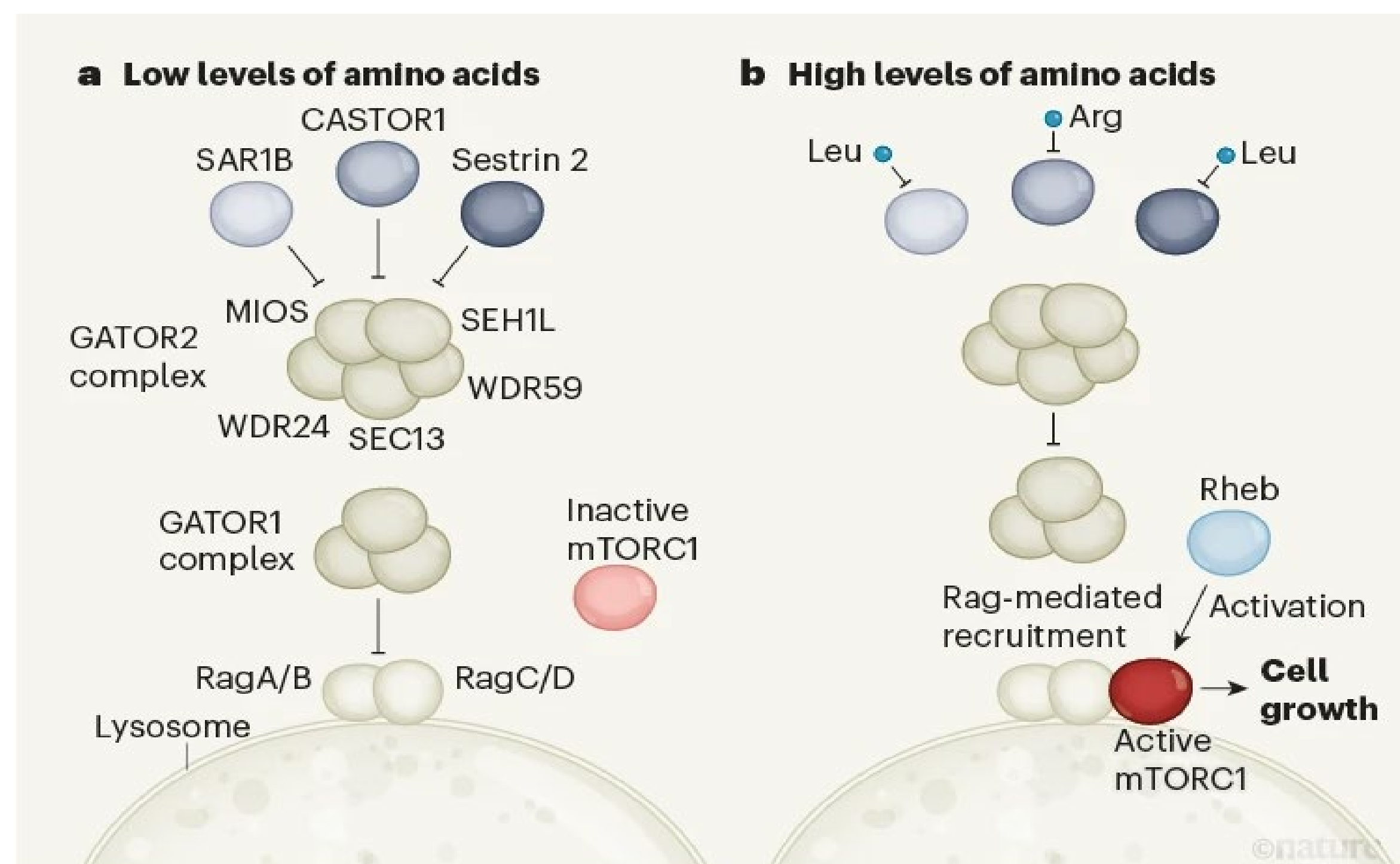


## BACKGROUND

- Cancer cells have a high demand for essential amino acids due to their rapid proliferation.
- Leucine (an essential amino acid) activates mTORC1 signaling, which promotes tumor growth and survival.
- The L-Type amino acid transporter (LAT) family (LAT1-4) facilitates essential amino acid transport into cells. LAT1 is frequently overexpressed in various cancers, promoting tumor growth and chemoresistance, making it a promising therapeutic target.
- The project aims to optimize the structure of ESK242 (a nonselective LAT1/LAT3 inhibitor) to develop a selective, noncompetitive LAT1 inhibitor.



## RESULTS

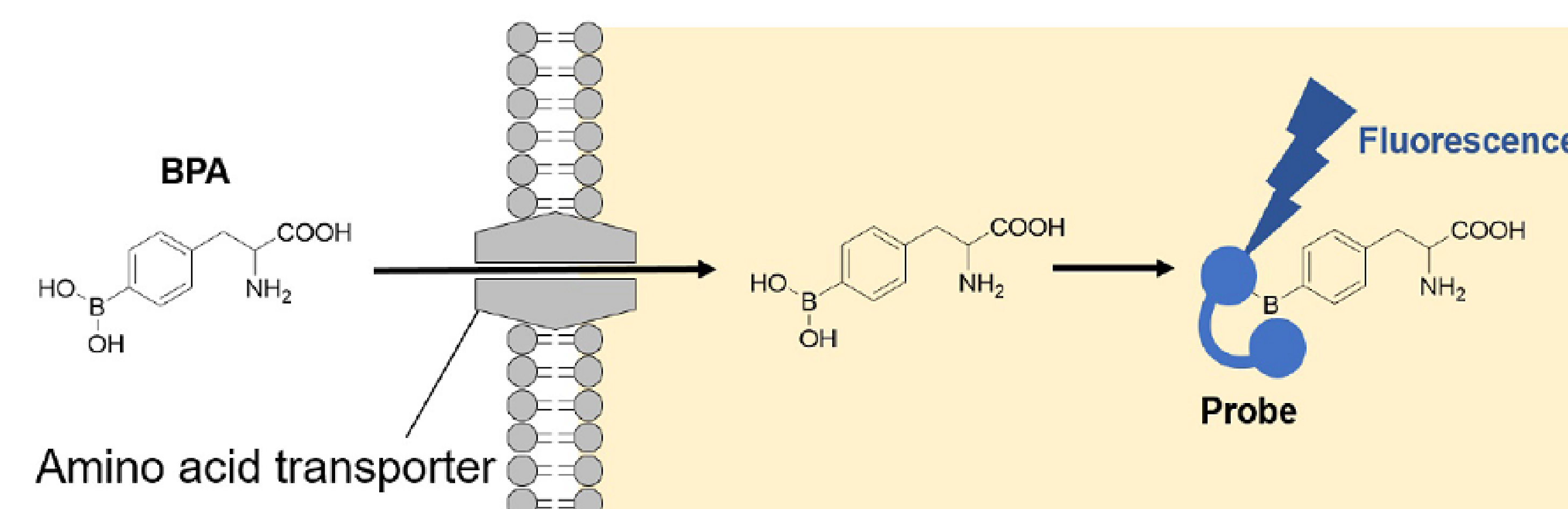
Compound	% inhibition			
	100 $\mu$ M			
	HeLa	MCF7	231	CHO
eLI1 (ESK246)	2%	8%	69%	35%
eLI2	57%	66%	85%	
eLI3 (ESK242)	73%	88%	74%	
eLI4	18%	-235%	39%	50%
eLI5	28%	-234%	93%	30%
eLI6	35%	-245%	62%	60%

## CONCLUSION

- Only eLI2 and eLI5 had improved percentage inhibition compared to ESK242 and this was only in one cell line (MDA-MB-231).
- However, no conclusions can be made on if the structural changes to ESK242 lead to increased LAT1 inhibitor activity due to the lack of selectivity of our current assay

## METHODS

- Structural replacements made to the angeolyl, fucose, or a-terpineol of ESK242.
- Characterized compounds with H-NMR and C-NMR.
- LAT1 activity was tested using in vitro LAT1 transporter assay in four cancer cell lines
- Measured fluorescence with microplate reader and calculated percent inhibition



## FUTURE PLANS

- Develop an assay with the cell line A549 with knockdown and overexpressed LAT1 so that we can accurately interpret what structural changes to ESK242 result in increased LAT1 activity.
- Synthesize more LAT1 inhibitors.

## LESSONS LEARNED

- The relative expression of the different LATs in the cell lines used for our assay are unknown.
- The amino acid we used in our assay (BPA) can be transported by all LATs
- To accurately interpret our assay results for LAT1 inhibitor activity, the assay needs to be optimized.